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# Factors influencing mortality trends of pancreatic cancer in Spain, 1955-2020

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**ABSTRACT**

**Objectives:** the aim of this study was to analyze the trends of pancreatic cancer mortality in Spain from 1955 to 2020 in both genders and every age group, in order to describe the changes in the prevalence of some risk factors and their possible influence on mortality.

**Methods:** direct standardized mortality rates were calculated using the World Standard Population 2000-2025 and joinpoint analysis was performed for age-specific and age-standardized mortality trends for the period 1955-2020.

**Results:** mortality rates increased with age in both genders, with a marked increase in older groups. During 2020, 71.5 % of male deaths and 81.5 % of female deaths from pancreatic cancer occurred among those aged 65 years or more. Spanish National Health Surveys since 1987 show decreasing trends in daily smoking, but striking increases in obesity and diabetes mellitus rates in both genders, and rates of daily smoking and obesity are remarkably higher among disadvantaged social classes.

**Conclusions:** pancreatic cancer mortality rates have increased uninterruptedly in Spain during the last decades. Increasing trends in obesity and diabetes mellitus, particularly among males, and the different prevalence of obesity and smoking according to social class are public health problems of

great concern. Smoking and obesity are potentially avoidable risk factors. Thus, educational programs and legislative measures should be implemented more widely, such as programs for smoking prevention, healthy nutrition and physical exercise, and would be applied more intensively in the most disadvantaged social classes.

**Keywords:** Pancreatic cancer. Trends. Incidence. Mortality. Spain. Risk factors.

## INTRODUCTION

There were 496,000 new cases of pancreatic cancer and 466,000 deaths worldwide in 2019 (2.6 % of all new cases of cancer and 4.7 % of all cancer deaths) and was the seventh leading cause of cancer death in both genders (1). It has been estimated that in Spain in 2021, there will be 4,571 new cases among males (2.88 % of all new cases of cancer among men) and 4,126 new cases among females (3.52 % of all new cases of cancer among women), with low five-year survival rates worldwide (rates in Spain of 6.7 % in men and 9.6 % in women) (2).

Risk factors for pancreatic cancer are largely unknown but major risk factors for developing pancreatic cancer include family history (3-5), obesity (6-10), type 2 diabetes (5,8,11), smoking (5,6,12,13) and age (14,15). Other risk factors are chronic pancreatitis and some gene mutations (5,6,14). Some studies show that an appropriate consumption of fresh fruit and vegetables may protect against pancreatic cancer (16).

Globally, the worldwide number of deaths and incident cases of pancreatic cancer has more than doubled from 1990 to 2017 (15), and in some countries it is projected to become the second-leading cause of cancer-related mortality by 2030 (6,17). These increasing incidence trends are attributed to remarkable changes in the prevalence of the aforementioned risk factors in developed countries, such as aging of the population and increasing rates of obesity and diabetes mellitus (DM) (18,19). During the last decades, there have been notable changes in the prevalence of these risk factors in Spain, first with an increase in the prevalence rate of smoking, and a subsequent decrease in tobacco consumption. Furthermore, there were striking increases in the prevalence of obesity and DM, with a progressive aging of the population (20). The aim of this study was to analyze the trends of pancreatic cancer mortality in Spain from 1955 to 2020 in both genders and every age group. The changes in the prevalence of some risk factors and their possible influence on mortality were described, in an attempt to identify the most appropriate measures to reduce the

frequency and lethality of this tumor.

## MATERIAL AND METHODS

Spanish population and mortality data were retrieved from the Spanish National Statistics Institute (Instituto Nacional de Estadística, INE) online public databases (21). The code used for the period 1955-1998 was 157 (7th, 8th and 9th Revision of the International Classification of Diseases [ICD7, ICD8 and ICD9]) and the code for the period 1999-2020 was C25 (10th Revision of the International Classification of Diseases [ICD10]). Mortality and resident population data for males and females were stratified yearly by 18 five-year age groups (from 0-4 years to 85 years or more). Total and sex-specific death rates for each quinquennial age group were computed for every calendar year and expressed as rates per 100,000 persons-years. All ages-standardized mortality rates that were truncated at 30-84 years per 100,000 persons-years were computed using the direct method and the World Health Organization (WHO) World Standard Population 2000-2025. Three-year moving averages were used to plot the age standardized mortality rates.

Joinpoint regression models were used for trend analysis (allowing up to three joinpoints), to identify significant changes in the linear slope (on a log scale) of age-standardized mortality rates and truncated standardized mortality rates from 1955 to 2020 (22). Annual percent change (APC) was estimated for each trend segment identified by the model and average annual percent change (AAPC) was estimated for the whole period (23). Increases or declines were considered to occur when the slope of the trend was found to be statistically different from zero (two-tailed $p < 0.05$).

Results of National Health Surveys (NHS) from 1987, 1993, 1995, 1997, 2001, 2003, 2006, 2011, 2014 and 2017 were obtained from the Spanish Ministry of Health, Consumption and Social Welfare (24). Data of daily smoking prevalence by age, gender, obesity (defined as body mass index [BMI] ≥ 30.0 kg/m$^2$) and its distribution by social class were also obtained from NHS Ministry's public databases.

The Ministry uses a classification of social class for their National Health Surveys, where social class I is directors and managers of establishments with ten or more employees and professionals traditionally associated with university degrees, and social class VI refers to unskilled workers. In this study, a comparison was made between social class I (higher) and social class VI (lowest) for two risk factors: obesity and daily smoking by age and gender in every NHS where this information was available.

The joinpoint analysis was performed with the Joinpoint Regression Program 4.9.0.0 (obtained from the Surveillance Research Program, National Cancer Institute). The handling of data, graphics and additional statistical analyses were performed with the STATA MP 14 software program.

**RESULTS**

Pancreatic cancer age-standardized mortality rates in males increased from 1.24 per 100,000 person-years in 1955 to 8.27 per 100,000 person-years in 2020, and among females from 1.29 per 100,000 person-years in 1955 to 5.68 per 100,000 person-years in 2020 (Fig. 1). The mortality males:females ratio rose from 0.74 in 1955 to 1.01 in 2020. Mortality rates increased with age in both genders, with a marked increase in older groups, as depicted in figure 2. During 2020, 71.5 % of male deaths and 81.5 % of female deaths from pancreatic cancer occurred among those aged 65 years or more. The results suggest that mortality trends have decreased in recent decades, particularly among those under 50 years of age.

Joinpoint analyses for age-specific and age-standardized mortality rates are shown in table 1. In males, there was an overall increase in the rates of 3 % per annum. Joinpoint analysis detected two change points (1962 and 1988). During the first period (1955-1962), rates increased by 11.07 % annually; during the second period (1962-1988) by 3.61 %; and by 0.88 % during the third period (1988-2020). In females, there was an overall increase in the rates of 2.6 % annually and joinpoint analysis also detected two change points (1963 and 1990), generating three periods: 1955-1963 (7.5 % annually), 1963-1990 (2.43 % annually) and 1990-2020 (1.42 % annually).

Among males, age-specific mortality rates increased in all age-groups (30-34 years old to 85 or more years old), with an AAPC of 2.0 % or more for men aged 35-39 to an AAPC of 3.9 % among those aged 85 years or more. Joinpoint analysis showed a statistically significant decrease in APCs among males aged from 35-44 from the 90s, but not among females.

Among females, age-specific mortality rates also increased in all age-groups, but AAPCs were lower than those among males, and an AAPC of 2.0 % or more began at 50-54 years of age. All-ages standardized mortality rates and truncated standardized mortality rates increased among males and females but with lower AAPCs among females.

Results of NHS about daily smokers are shown in table 2. The results of ten health surveys, from 1987 to 2017, show the prevalence of daily smoking by age and gender. The prevalence of daily smokers decreased in both genders but with different slopes; declining steadily in males, but first

increasing and later decreasing among females. The results show a reduced rate among males during the period 1987-2017 of 52.5 % but 13.7 % among females. The results of NHS about obesity are shown in figure 3, demonstrating notable increases in the prevalence of obesity in both genders during the period 1993-2017.

In the 1987 NHS, 3.12 % of males and 4.74 % of females reported having DM. In the following NHS, the prevalence rates increased progressively, and in 2017 the rates were 10.65 % in males and 9.11 % in females, that is, the prevalence of DM had tripled in men and doubled in women compared to 1987. According to the results of the NHS, the trends in obesity and daily smoking rates showed striking differences in both genders and in all age groups according to social class, being much higher among social class VI (Table 3).

**DISCUSSION**

Mortality rates from pancreatic cancer increased in Spain from 1955 to 2020 in both genders. This rise is attributable to progressive aging of the population and increasing rates of tobacco smoking, obesity and DM. The role of chronic pancreatitis in these trends is probably much smaller, as the cumulative risk of pancreatic cancer among those with chronic pancreatitis is 1.8 % after ten years and 4 % at 20 years (25).

The slower increase in pancreatic cancer mortality rates from 1988 to 2020 in males (APC 0.88 %) and from 1989 to 2020 in females (APC 1.42 %) could be caused by the decline in tobacco consumption. In Spain, the prevalence of daily smoking among males steadily decreased since the 80s while in females it rose until the late 90s and then decreased. These differences could explain their different AAPCs (0.88 % *vs* 1.42 %). These different trends may also explain the negative trends in APC from the late 90s to 2020 among males aged < 50 years, which was not found among females. Among older people, the impact of the decline in smoking prevalence was not so marked, probably due to its cumulative effects during the decades of heavy consumption.

The trends in obesity and DM prevalence rates in both sexes and in all age groups in Spain probably explain its upward trends, despite the decline in tobacco use. Otherwise, individuals with the longest duration of obesity have the highest risk of pancreatic cancer, particularly among individuals who were overweight at a younger age. Thus, efforts to prevent childhood and youth obesity seem essential (26,27).

The accuracy of Spanish cancer death certificates has been studied, and deaths from cancer as a whole and leading cancer types, such as cancer of the pancreas, are well certified (28). Moreover, it is unlikely that the change from ICD9 codes to ICD10 implemented in 1999 has had an impact on the reliability of Spanish mortality data, as the codes are very similar, and trends in the leading causes of death have not been greatly affected by the revisions in ICD10 (29).

Diagnostic procedures have improved dramatically from 1955 to the present day. For example, techniques such as computerized tomography were not implemented until the late 1970s and did not spread to a majority of centers until the 1980s. Therefore, an underestimation of pancreatic cancer diagnosis in previous years cannot be ruled out.

The US Preventive Services Task Force found no evidence that screening for pancreatic cancer or the treatment of screen-detected pancreatic cancer improves disease-specific morbidity or mortality, or all-cause mortality. Furthermore, the previous recommendation against screening for pancreatic cancer in asymptomatic individuals was confirmed (30,31).

Although survival in pancreatic cancer is still disappointingly low, a moderate improvement (slightly higher in men) has been described in some countries in the last years, which could have slowed the increase in the mortality rates since the 90s (32). Multimodality therapy with effective surgery, chemotherapy and radiation are generally needed to optimize long-term outcomes. While advances in surgery have led to improved outcomes in recent decades, the development of more effective systemic therapies based on improved molecular approaches will be necessary to make further strides in pancreatic cancer care (33). Multidisciplinary teams need to be formed for the best use of existing resources in order to improve current results, focusing on early diagnosis, applying more refined surgical techniques, greater attention to perioperative and postoperative care and the application of novel chemotherapy and even radiotherapy treatment protocols (34). For example, recent randomized controlled trials have shown promising results with neoadjuvant chemotherapy with folfirinox or gemcitabine in borderline resectable tumors (33,35).

Social class is associated with the prevalence of daily smoking, and NHS show that the prevalence of daily smoking and obesity among male and female unqualified workers (social class VI) is remarkably higher than that among high-qualified professionals (social class I). Another frequent problem in the most disadvantaged social classes is the delay in attending healthcare services in case of illness. Thus, the implementation of preventive measures aimed at reducing the incidence and mortality of pancreatic cancer should be offered with a greater emphasis on the most

disadvantaged social classes.

These results need to be interpreted with caution. This study is limited by its ecological nature and the assumption that the higher prevalence of the risk factors found in other studies are also high among Spanish patients with this disease. Our results attempt to help identify trends and generate etiological hypotheses, but do not provide any direct evidence of the role of specific exposures such as obesity, diabetes, smoking and social class. However, these results highlight the need for epidemiologic research to elucidate the causes of the increase in the incidence and mortality of pancreatic cancer in Spain, as well as to reinforce strategies to improve early diagnosis and treatment, curb the epidemic of smoking and obesity and shift the Spanish population towards a healthier diet and more active lifestyle. Research on procedures for early diagnosis and promising treatments such as neoadjuvant chemotherapy are also priorities to improve the low survival rates of this disease.

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**Table 1. Joinpoint analysis of trends in age-specific mortality rates, age-standardized mortality rates (Age-std) and truncated age-standardized 30-84 years mortality rates (Trunc-std) of pancreatic cancer in Spain, by gender, from 1955 to 2010**

| *Gender* | *Age group* | *Joinpoints* | *AAPC* | *APC period 1* | *APC period 2* | *APC period 3* |
|---|---|---|---|---|---|---|
| Males | | | | | | |
| | 30-34 | 0 | 0.43 | 1955-2020: 0.43 | | |
| | 35-39 | 2 | 2.2* | 1955-1960: 29.97* | 1960-1990: 2.22* | 1990-2020: -1.83* |
| | 40-44 | 2 | 2.0* | 1955-1962: 14.39* | 1962-1996:2.62* | 1996-2020: -2.21* |
| | 45-49 | 2 | 2.5* | 1955-1959: 24.97* | 1959-2001: 2.47* | 2001-2020: -1.51 |
| | 50-54 | 2 | 2.5* | 1955-1963: 9.75* | 1963-1999: 2.55* | 1999-2020: -0.34 |
| | 55-59 | 2 | 2.9* | 1955-1961: 15.20* | 1961-1995: 2.78* | 1995-2020: 0.35 |
| | 60-64 | 2 | 3.0* | 1955-1963: 11.0* | 1963-1990: 2.93* | 1990-2020: 1.11* |
| | 65-69 | 2 | 3.0* | 1955-1962: 10.77* | 1962-1985: 3.77* | 1985-2020: 1.10* |
| | 70-74 | 2 | 3.3* | 1955-1960: 13.74* | 1960-1984: 4.19* | 1984-2020: 1.29* |
| | 75-79 | 2 | 3.4* | 1955-1968: 8.74* | 1968-1987: 3.80* | 1987-2020: 1.08* |
| | 80-84 | 1 | 3.1* | 1955-1988: 5.08* | 1988-2020: 1.01* | |
| | 85+ | 1 | 3.9* | 1955-1985: 7.36* | 1985-2020: 1.02* | |
| | Age-std | 2 | 3.0* | 1955-1962: 11.07* | 1962-1988: 3.61* | 1988-2020: 0.88* |
| | Trunc-std | 2 | 3.0* | 1955-1962: 10.93* | 1962-1988: 3.50* | 1988-2020: 0.88* |
| Females | | | | | | |
| | 30-34 | 0 | 0.48 | 1955-2020: 0.48 | | |
| | 35-39 | 0 | 0.88* | 1955-2020: 0.88* | | |
| | 40-44 | 2 | 0.9 | 1955-1979: -1.01 | 1979-1994: 5.30* | 1994-2020: 0.23 |
| | 45-49 | 0 | 1.84* | 1955-2020: 1.84* | | |
| | 50-54 | 1 | 2.2* | 1955-1962: 6.37 | 1962-2020: 1.68* | |
| | 55-59 | 1 | 2.4* | 1955-1962: 7.89* | 1962-2020: 1.81* | |
| | 60-64 | 1 | 2.3* | 1955-1963: 7.79* | 1963-2020: 1.60 | |
| | 65-69 | 1 | 2.5* | 1955-1965: 6.60* | 1965-2020: 1.75* | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 70-74 | 2 | 3.0* | 1955-1961: 15.63* | 1961-1987: 2.45* | 1987-2020: 1.28* |
| | 75-79 | 2 | 2.8* | 1955-1969: 6.43* | 1969-1988: 2.71* | 1988-2020: 1.29* |
| | 80-84 | 1 | 2.8* | 1955-1985: 4.74* | 1985-2020: 1.24* | |
| | 85+ | 1 | 3.1* | 1955-1993: 4.70* | 1993-2020: 0.96* | |
| | Age-std | 2 | 2.6* | 1955-1963: 7.50* | 1963-1990: 2.43* | 1990-2020: 1.42* |
| | Trunc-std | 2 | 2.5* | 1955-1963: 7.68* | 1963-1989: 2.25* | 1989-2020: 1.46* |

AAPC: annual average percent change; APC: annual percent change. *$p < 0.05$.

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**Table 2. Prevalence of daily smoking in Spain by age and gender. Results of NHS 1987 to 2017**

| *Gender* | *NHS* | *Age groups* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 15-24 | 25-34 | 35-44 | 45-54 | 55-64 | 65-74 | 75 or more | All |
| Males | | | | | | | | | |
| | 1987 | 55.22 | 66.04 | 59.52 | 55.98 | 48.33 | 36.78 | 27.89 | 53.87 |
| | 1993 | 38.60 | 57.92 | 57.47 | 48.41 | 37.37 | 22.36 | 16.29 | 43.98 |
| | 1995 | 38.95 | 56.01 | 52.31 | 45.08 | 40.88 | 30.14 | 14.20 | 43.50 |
| | 1997 | 35.95 | 53.42 | 57.69 | 48.92 | 34.33 | 22.76 | 15.12 | 42.11 |
| | 2001 | 36.48 | 48.05 | 52.02 | 43.43 | 35.57 | 19.46 | 13.42 | 39.21 |
| | 2003 | 34.74 | 38.65 | 44.39 | 41.81 | 26.82 | 18.99 | 8.56 | 34.15 |
| | 2006 | 24.96 | 40.16 | 37.41 | 38.83 | 28.45 | 18.64 | 8.93 | 31.56 |
| | 2011 | 22.48 | 35.68 | 32.83 | 34.34 | 26.26 | 16.16 | 7.91 | 27.87 |
| | 2014 | 21.43 | 35.09 | 32.74 | 33.57 | 28.56 | 16.38 | 8.24 | 27.57 |
| | 2017 | 19.96 | 32.89 | 32.45 | 29.43 | 26.07 | 16.51 | 7.66 | 25.58 |
| Females | | | | | | | | | |
| | 1987 | 48.44 | 44.82 | 21.11 | 6.33 | 3.16 | 1.85 | 1.55 | 21.75 |
| | 1993 | 33.83 | 41.32 | 27.66 | 11.73 | 5.40 | 1.63 | 1.54 | 20.77 |
| | 1995 | 40.54 | 46.94 | 32.40 | 14.19 | 7.27 | 2.10 | 0.48 | 24.51 |
| | 1997 | 34.48 | 50.16 | 35.34 | 17.94 | 5.68 | 1.67 | 0.90 | 24.77 |
| | 2001 | 36.92 | 40.32 | 39.55 | 22.76 | 8.18 | 2.45 | 0.56 | 24.65 |
| | 2003 | 31.10 | 34.13 | 36.02 | 25.51 | 7.54 | 2.36 | 0.81 | 22.39 |
| | 2006 | 28.93 | 30.16 | 30.73 | 28.47 | 11.77 | 3.86 | 1.37 | 21.51 |
| | 2011 | 20.95 | 28.26 | 28.25 | 29.97 | 15.35 | 4.58 | 0.76 | 20.22 |
| | 2014 | 15.46 | 24.84 | 24.52 | 26.42 | 20.82 | 6.74 | 1.24 | 18.60 |
| | 2017 | 15.05 | 24.31 | 24.82 | 26.37 | 22.16 | 7.82 | 2.01 | 18.76 |

Results shown as a percentage.

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**Table 3. Obesity and daily smoking in Spain. Comparison between social class I and VI by age group and gender. Results of NHS from 2001 to 2017**

| *Obesity* | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| *Age group* | *Gender* | *Social class* | *2001* | *2003* | *2006* | *2011* | *2014* | *2017* |
| 25-44 | Males | I | 5.93 | 10.01 | 12.17 | 7.85 | 9.74 | 8.56 |
| | | VI | 16.73 | 14.70 | 12.65 | 15.43 | 14.31 | 14.41 |
| | Females | I | 3.29 | 1.72 | 2.93 | 4.22 | 3.05 | 4.0 |
| | | VI | 9.76 | 15.77 | 15.67 | 16.05 | 21.12 | 19.19 |
| 45-64 | Males | I | 13.18 | 10.31 | 17.72 | 14.64 | 15.95 | 13.77 |
| | | VI | 14.31 | 20.67 | 23.59 | 26.57 | 25.02 | 25.04 |
| | Females | I | 3.42 | 11.34 | 7.90 | 6.17 | 4.93 | 7.20 |
| | | VI | 27.88 | 27.78 | 24.03 | 22.17 | 23.22 | 23.31 |
| 65 or more | Males | I | 18.30 | 13.24 | 17.12 | 19.0 | 13.9 | 14.58 |
| | | VI | 13.48 | 18.53 | 22.46 | 27.19 | 24.76 | 23.43 |
| | Females | I | - | 10.02 | 19.51 | 4.03 | 5.89 | 15.95 |
| | | VI | 33.09 | 24.40 | 28.57 | 29.04 | 30.31 | 32.05 |
| *Daily smokers* | | | | | | | | |
| *Age group* | *Gender* | *Social class* | *2001* | *2003* | *2006* | *2011* | *2014* | *2017* |
| 25-44 | Males | I | 39.14 | 29.99 | 24.95 | 16.13 | 21.58 | 15.53 |
| | | VI | 55.31 | 48.35 | 41.85 | 41.36 | 41.38 | 45.52 |
| | Females | I | 32.37 | 21.19 | 18.73 | 20.53 | 14.3 | 12.02 |
| | | VI | 47.34 | 40.61 | 32.54 | 28.61 | 25.88 | 30.22 |
| 45-64 | Males | I | 38.88 | 25.18 | 20.1 | 22.98 | 18.99 | 15.6 |
| | | VI | 49.69 | 38.42 | 38.2 | 37.46 | 37.13 | 30.81 |
| | Females | I | 36.64 | 27.88 | 25.71 | 26.63 | 22.16 | 16.03 |
| | | VI | 16.12 | 13.13 | 22.3 | 24.61 | 26.47 | 25.81 |
| 65 or more | Males | I | 11.7 | 12.54 | 11.61 | 14.05 | 15.3 | 11.39 |
| | | VI | 18.95 | 16.15 | 14.58 | 11.08 | 14.25 | 15.49 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Females | I | - | 11.78 | 14.13 | 10.33 | 10.4 | 11.09 |
| | | VI | 2.82 | 0.47 | 1.57 | 1.37 | 2.42 | 4.2 |

Prevalence rates in percentage. Obesity and social class definitions in text.

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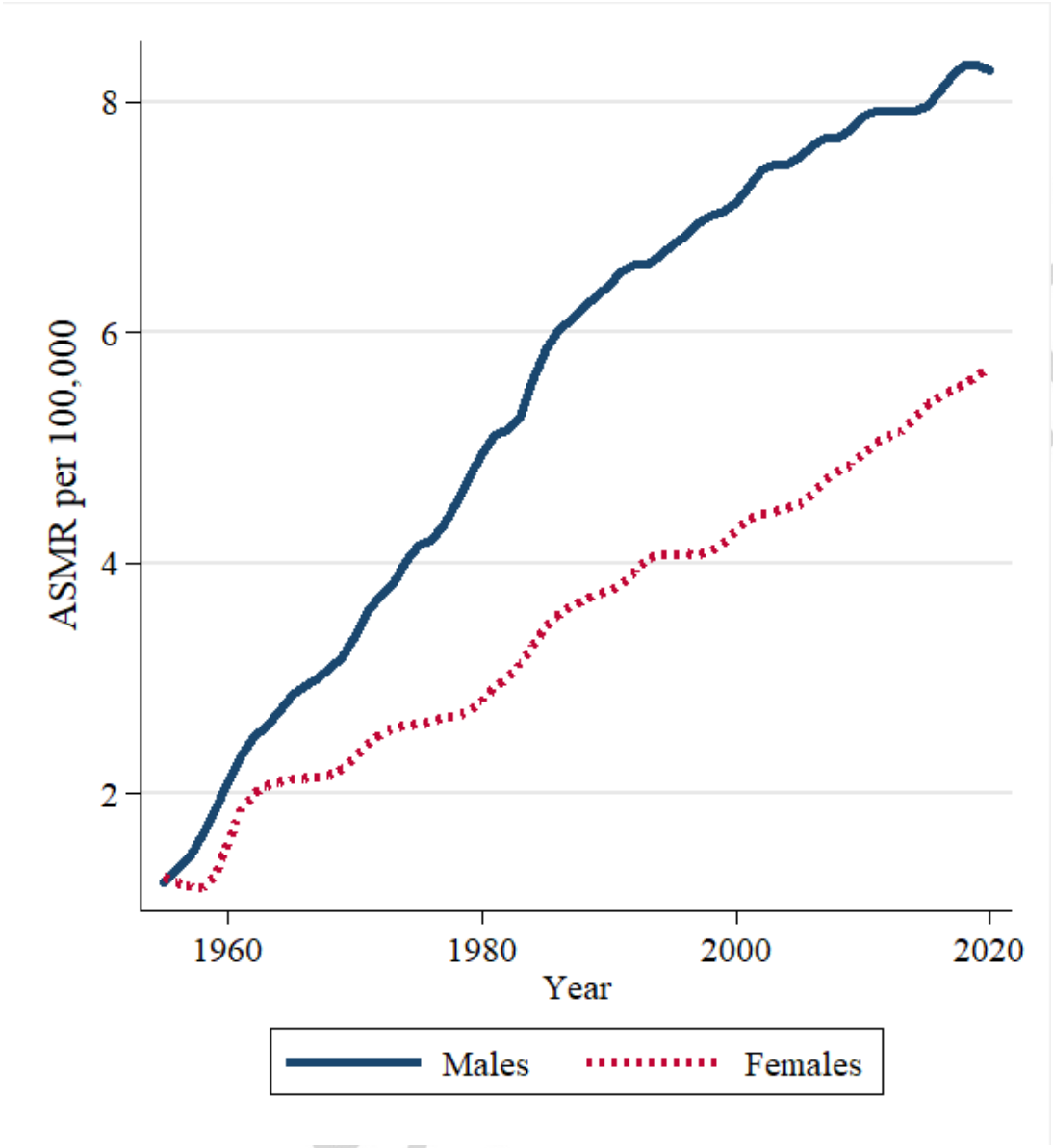


Fig. 1. Age-standardized mortality rates (ASMR) per 100,000 in Spain, by gender from 1955-2020.

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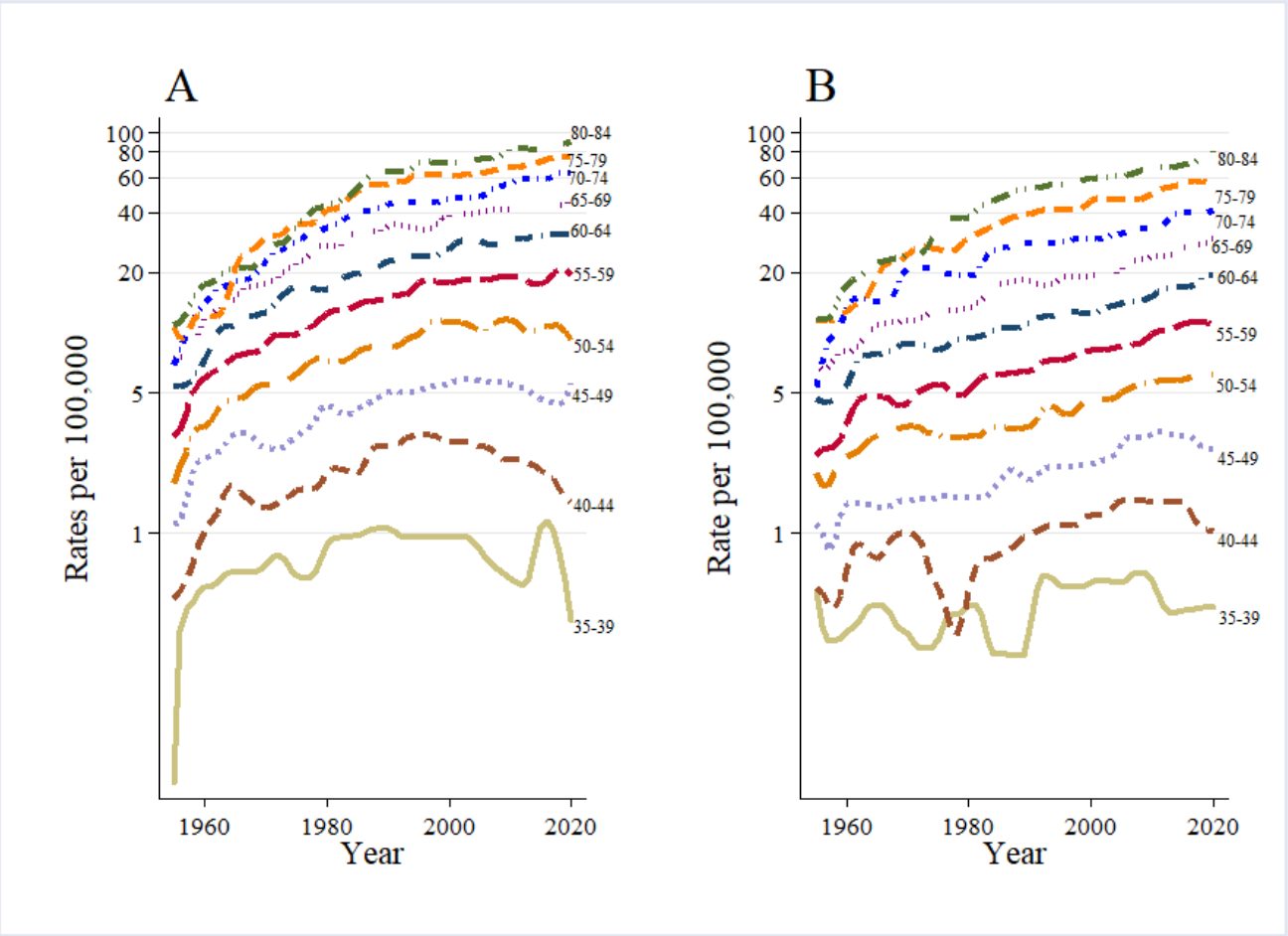


Fig. 2. Age-specific mortality rates per 100,000 in Spain, by gender from 1955 to 2020. A. Males. B. Females.

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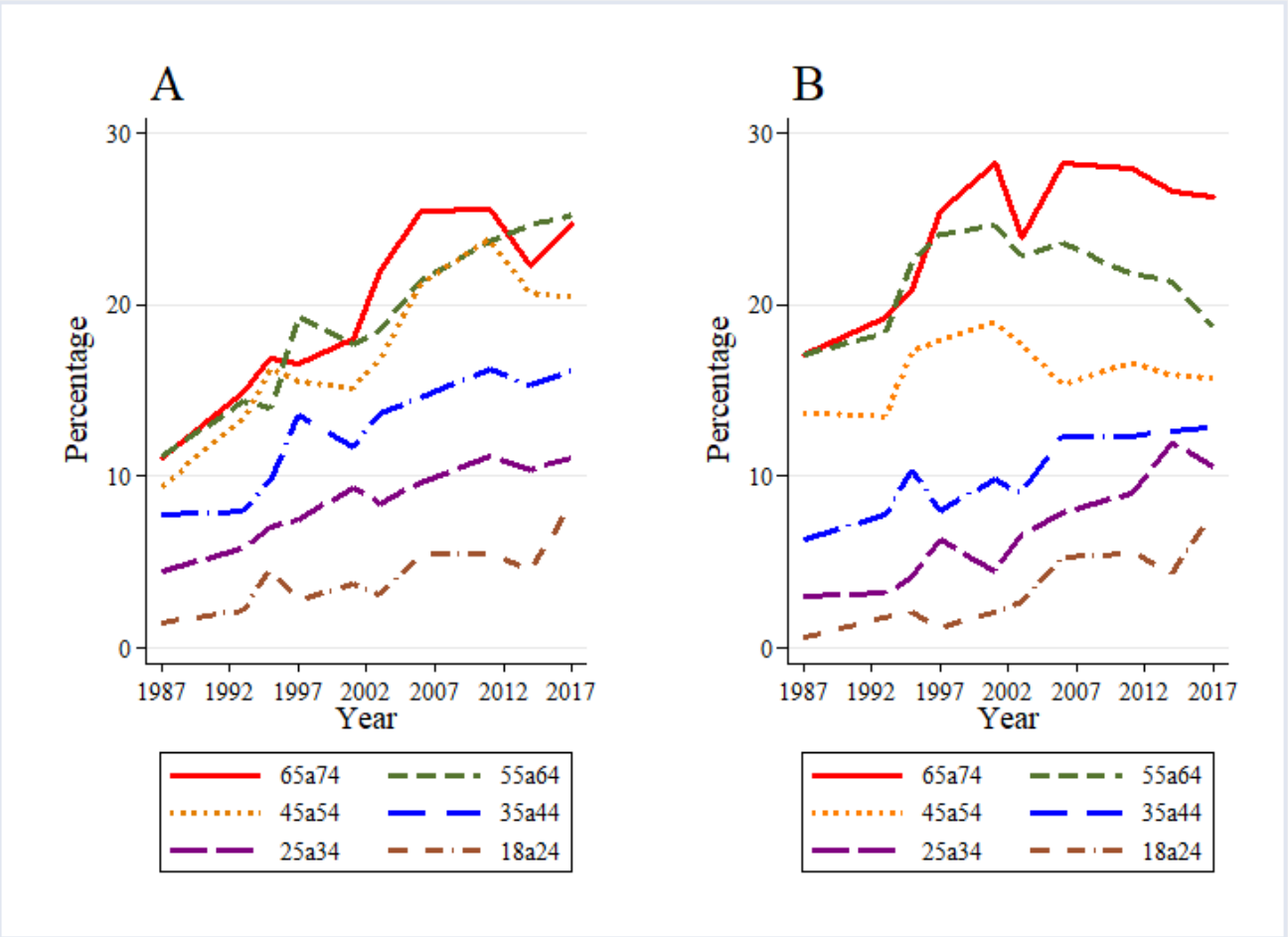


Fig. 3. Age-specific obesity rates by gender. Spanish NHS 1987-2017. A. Males. B. Females.